In-vitro profile of a new β-lactam, ceftobiprole, with activity against methicillin-resistant *Staphylococcus aureus*

M. E. Jones

Eurofins Medinet (Anti-Infective Services) Inc., Herndon, Virginia, USA

ABSTRACT

Ceftobiprole is a novel, broad-spectrum cephalosporin with in-vitro activity against common Gram-positive and Gram-negative organisms. It forms a stable inhibitory complex with *Staphylococcus aureus* penicillin-binding protein (PBP) 2′ (2a), resulting in enhanced activity against methicillin-resistant *S. aureus* (MRSA). In recent studies of methicillin-susceptible *S. aureus*, the ceftobiprole MIC_{90} value was most frequently ≤1.0 mg/L (MIC range ≤0.25–1.0 mg/L). For MRSA, MIC_{90} values were generally 2.0 mg/L (MIC range ≤0.06–4.0 mg/L). MICs for all streptococcal species, except penicillin-resistant *Streptococcus viridans* but including penicillin-resistant *Streptococcus pneumoniae*, ranged from ≤0.008 to 2.0 mg/L. Ceftobiprole is active against *Enterococcus faecalis* ($MIC_{90} = 4$ mg/L), but not generally active against *Enterococcus faecium* ($MIC_{90} > 16$ mg/L). Ceftobiprole displayed bactericidal activity against Gram-negative pathogens comparable to that of cefepime, ceftazidime or piperacillin–tazobactam in early studies. However, recent data show activity against *Pseudomonas aeruginosa* similar to that of cefepime but less than that of ceftazidime. Ceftobiprole, like cefepime, is stable in the presence of most class A non-extended spectrum β-lactamases and inducible class C β-lactamases. Ceftobiprole is a poor inducer of AmpC β-lactamase and a poor substrate for hydrolysis by AmpC β-lactamase. Studies of ceftobiprole in several animal models have demonstrated potent in-vivo efficacy against infections caused by MRSA, including strains intermediately resistant to vancomycin. It was also efficacious in murine infections caused by Gram-negative bacteria with MIC values ≤2 mg/L. The broad spectrum of activity demonstrated by ceftobiprole *in vitro* and *in vivo* suggests that it may have potential for empirical treatment of suspected Gram-negative and Gram-positive infections, including those caused by MRSA.

Keywords Ceftobiprole, *in vivo*, *in vitro*, MRSA, PBP2′

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INTRODUCTION

Ceftobiprole is a novel cephalosporin with broad-spectrum activity against most clinically relevant bacterial pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA). This bactericidal agent, delivered as a prodrug, ceftobiprole medocaril, has recently been shown to be clinically and microbiologically effective on the basis of preliminary data from phase III clinical studies [1].

Corresponding author and reprint requests: M. E. Jones, Eurofins Medinet (Anti-Infective Services) Inc., 13665 Dulles Technology Drive, Herndon, VA 20171, USA
E-mail: mark.jones@eurofinsmedinet.com

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The availability of antibiotics with anti-MRSA activity is critical because the prevalence of MRSA infections is increasing worldwide. Surveillance data from the TSN Database USA (Eurofins Medinet, Inc.) illustrate this growing prevalence in the USA among inpatients, and especially those in the intensive care unit. For example, among the sub-population aged 64 years or more, the proportion of MRSA isolates has increased over the past decade and now comprises 60–70% of all isolates (Fig. 1). The percentage of outpatients with infections caused by MRSA has also increased and directly correlates with the rate of MRSA infection among inpatients at a given hospital [2]. This signifies that MRSA is no longer confined to hospitals but is also a problem within the community, especially in so-called healthcare-associated infections.

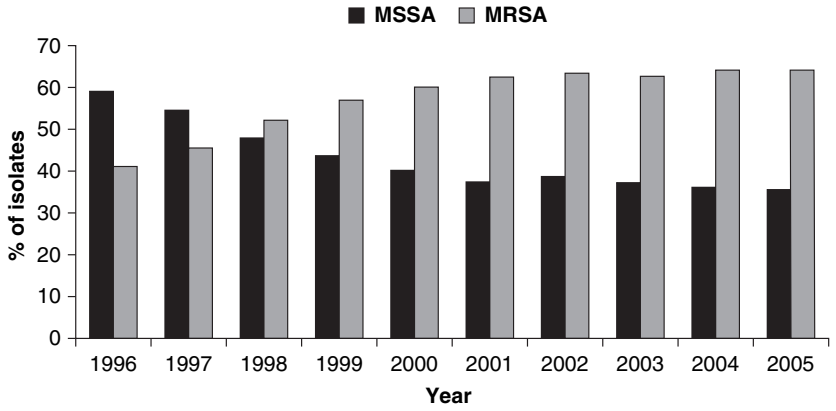

Fig. 1. Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) in the USA among clinical specimens from inpatients/intensive care unit patients aged >64 years (n = approximately 4000–38 000 isolates per year) (TSN Database USA, Eurofins Medinet, Inc.).

Ceftobiprole is a novel member of the cephalosporin family of antibiotics with demonstrated activity against MRSA. The cephalosporins have played a critical role in healthcare since 1953, and the clinical utility of this class has evolved with each new generation or group. For example, cefotaxime, ceftriaxone and cefuroxime, classified as group 4 cephalosporins according to the Bryskier system [3], are broad-spectrum compounds but lack activity against the non-fermenting Gram-negative organisms, and are hydrolysed slowly by AmpC β-lactamases produced by some enterobacteriaceae. By comparison, the more recently developed cephalosporins cefepime and cefpirome, classified as group 6, have an extended spectrum of activity, including *Pseudomonas aeruginosa*, and a lower affinity for chromosomal β-lactamases. These properties result in a marked advantage against resistant mutants of several species producing either derepressed class C chromosomal β-lactamases or variant class A β-lactamases [4]. Because of these qualities and their history of safety and tolerability, cephalosporins are the most widely used class of antibiotic in the hospital setting. However, all currently available β-lactam antibiotics are considered to be clinically inactive against MRSA [5].

Ceftobiprole has not yet been classified according to the Bryskier system. Nevertheless, its bactericidal activity against MRSA and *Enterococcus faecalis*, at concentrations that are therapeutically achievable, sets it apart from other cephalosporins, signifying potential clinical utility, especially during this time of increasing MRSA prevalence. The potent anti-MRSA activity of ceftobiprole is attributable to a mechanism of action similar to that of all other β-lactam molecules; that is, ceftobiprole prevents formation of a new cell wall in dividing bacteria, eventually leading to cell lysis, through binding and inhibiting penicillin-binding proteins (PBPs). The critical differentiating feature of ceftobiprole is its apparent high-affinity interaction with PBP2′ (2a) of methicillin-resistant staphylococci, the PBP that is responsible for resistance to other β-lactam antibiotics [6].

IN-VITRO ACTIVITY AGAINST GRAM-POSITIVE COCCI

Ceftobiprole exhibits potent bactericidal activity *in vitro* against most clinically relevant streptococci and staphylococci, including penicillin-resistant strains of pneumococcus and MRSA. In-vitro susceptibility of staphylococci to ceftobiprole has been evaluated in a number of different studies (Table 1) [6–9] (15th ECCMID, abstract

Table 1. Summary of in-vitro susceptibility of staphylococci to ceftobiprole

Staphylococci tested	Total	MIC range (mg/L)	MIC_{90} (mg/L)
MRSA[a,b] [8,9]	925	0.06–2	2
MSSA[a] [8,9]	248	0.25–2	0.5
VISA [8]	18	0.25–4	–
VRSA [7,8]	2	2	–
MSCoNS[a] [8,9]	72	≤0.015–1	1
MRCoNS[a] [8,9]	327	≤0.015–8	2

[a]44th ICAAC, abstract E-2021).
[b]15th ECCMID, abstract P-1570.
MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; VISA, intermediately vancomycin-resistant *S. aureus*; VRSA, vancomycin-resistant *S. aureus*; MSCoNS, methicillin-susceptible/coagulase-negative staphylococci; MRCoNS, methicillin-susceptible/coagulase-negative staphylococci.

P-1570). On the basis of cumulative data from these studies, MICs for methicillin-susceptible *S. aureus* (MSSA) strains ($n = 248$) had a distribution of 0.25–2 mg/L, and the MIC_{90} was 0.5 mg/L. Given the importance of MRSA, the activity of ceftobiprole was measured against an even greater number of isolates, totalling 925. MIC values ranged from 0.06 mg/L to 2 mg/L, with an MIC_{90} of 2 mg/L. Because 100% of MRSA isolates were susceptible at MIC values of ≤4 mg/L, ceftobiprole has demonstrated greater in-vitro activity against this resistant pathogen than all currently marketed β-lactams.

These results are supported by an ongoing study of ceftobiprole activity against recent clinical isolates of *S. aureus* obtained from patients with complicated skin and skin structure infections (44th ICAAC, abstract E-2021). Among the 230 MRSA isolates from this trial, the MIC distribution was 0.5–2 mg/L. The MIC distribution of more than 300 MSSA was 0.12–1 mg/L.

Ceftobiprole is also effective against other *Staphylococcus* strains with reduced susceptibility to commonly used antibiotics [6–9] (15th ECCMID, abstract P-1570). Resistance to the glycopeptide vancomycin, an important anti-MRSA drug, has now been reported in isolated patients [10,11]. MIC distributions of ceftobiprole against 18 intermediately vancomycin-resistant *S. aureus* isolates (0.25–4 mg/L) and two vancomycin-resistant *S. aureus* isolates (2 mg/L) are similar to those of vancomycin-susceptible MRSA isolates (Table 1) [8], suggesting that decreased susceptibility to vancomycin has a negligible effect on ceftobiprole activity. Activity against coagulase-negative staphylococci has also been evaluated, since these bacteria are a major cause of nosocomial infections and are often resistant to multiple antibiotics. The MIC distribution for methicillin-susceptible/coagulase-negative staphylococci strains was ≤0.015–1 mg/L ($MIC_{90} = 1$ mg/L), and for methicillin-resistant/coagulase-negative staphylococci it was ≤0.015–8 mg/L ($MIC_{90} = 2$ mg/L) (Table 1).

The anti-MRSA activity of ceftobiprole has been compared to that of other agents in a number of studies [6–9] (44th ICAAC, abstract E-2021). On the basis of MIC_{90} values, ceftobiprole has anti-staphylococcal activity similar to that of vancomycin and linezolid ($MIC_{90} = 2$ mg/L for all three agents) and activity superior to that of ciprofloxacin and erythromycin (both $MIC_{90} > 32$ mg/L), clindamycin ($MIC_{90} = 16$ mg/L) and other β-lactams ($MIC_{90} > 32$ mg/L for cefotaxime, ceftriaxone, cefepime, and meropenem). The bactericidal activity of ceftobiprole against *S. aureus*, based on the killing rate against *S. aureus* ATCC 25923, is shown in Fig. 2. Bactericidal activity measured over 24 h was rapid at 0.5–5.0 × MIC [6]. Vancomycin compared less favourably, demonstrating bactericidal activity after 24 h only at 5.0 × MIC.

The broad-spectrum activity of ceftobiprole also encompasses streptococci, including strains of *Streptococcus pneumoniae* and enterococci. With regard to enterococci, ceftobiprole activity is similar to that of other cephalosporins. MIC values ranged from 0.12 to 2 mg/L for 33 *Enterococcus faecalis* isolates, including ampicillin-susceptible, vancomycin-resistant *Enterococcus faecalis* strains (44th ICAAC, abstract E-2021). However,

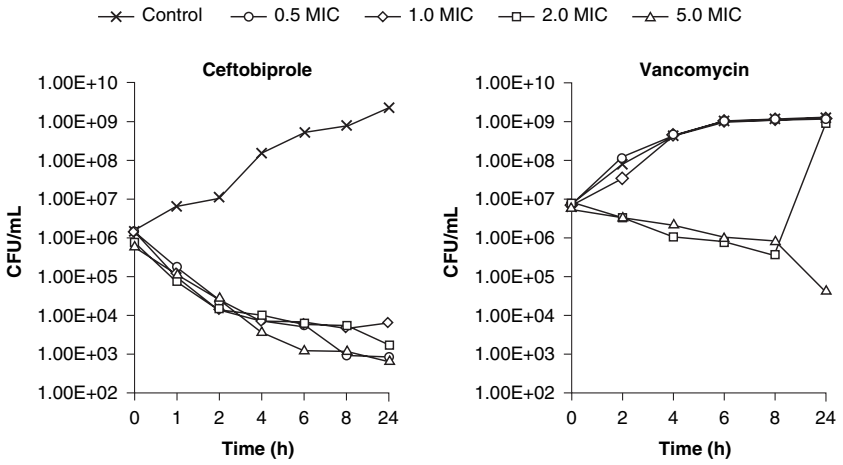

Fig. 2. The bactericidal activities of ceftobiprole and vancomycin against methicillin-susceptible *Staphylococcus aureus* ATCC 25923 over 24 h. Reproduced from Hebeisen *et al*. [6] with permission.

ceftobiprole generally demonstrated poor activity against *Enterococcus faecium*, with MIC values of 2 or >8 mg/L for a small number of tested isolates [12].

Activity against *S. pneumoniae*, including penicillin-resistant strains, was demonstrated in a study of 299 clinical isolates [13] using agar dilution to determine MIC values against penicillin-susceptible, intermediately penicillin-resistant and penicillin-resistant strains. Ceftobiprole had the lowest MIC_{90} values compared to other β-lactams tested, including cefepime, ceftriaxone, penicillin and amoxycillin (Fig. 3). MIC_{90} values for ceftobiprole were 0.016 mg/L for penicillin-susceptible strains (MIC distribution 0.008–0.03 mg/L), 0.5 mg/L for penicillin-intermediate strains (0.008–1 mg/L), and 1 mg/L for penicillin-resistant strains (0.016–4 mg/L). By comparison, MIC_{90} values for the other β-lactams against penicillin-resistant strains were 2–8 times higher (2 mg/L, cefepime and ceftriaxone; 16 mg/L, cefuroxime; 4 mg/L, penicillin; and 8 mg/L, amoxycillin). Thus, ceftobiprole had the lowest MIC values among the six β-lactams tested against pneumococci and was active against strains resistant to other agents, including multidrug-resistant strains.

IN-VITRO ACTIVITY AGAINST GRAM-NEGATIVE BACILLI

In addition to being active against resistant Gram-positive pathogens, ceftobiprole demonstrates activity against clinically important Gram-negative bacteria. Heep *et al*. (15th ECCMID, abstract P-1569) measured in-vitro activity against Enterobacteriaceae using 372 clinical isolates from respiratory infections among hospitalised patients in the USA and Europe. Isolates comprised the most common Enterobacteriaceae species, including

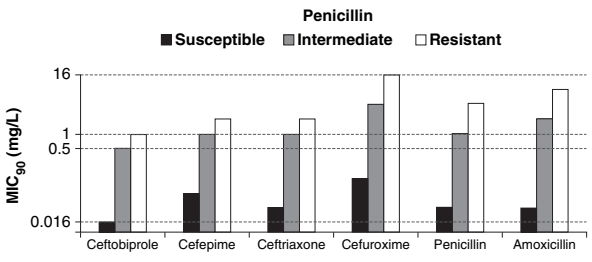

Fig. 3. Comparison of β-lactam MIC values against *Streptococcus pneumoniae* ($n = 300$) [13].

Escherichia coli ($n = 60$), *Serratia marcescens* ($n = 62$), *Klebsiella pneumoniae* ($n = 60$), *Enterobacter cloacae* ($n = 60$), *Enterobacter aerogenes* ($n = 17$), *Citrobacter freundii* ($n = 20$), *Citrobacter koseri* ($n = 7$), *Klebsiella oxytoca* ($n = 25$), and *Proteus mirabilis* ($n = 61$). These included strains that produce extended-spectrum β-lactamases (ESBLs). MIC values, determined by broth microdilution, were similar for ceftobiprole, ceftazidime and cefepime, with MIC_{90} values of 4, 32 and 1 mg/L, respectively. At an MIC of 4 mg/L, ceftobiprole inhibited the growth of 92.2% of the strains tested.

Fig. 4 illustrates these data as cumulative percentages of Enterobacteriaceae inhibited at different cephalosporin MIC values (15th ECCMID, abstract P-1569). Inclusion of all 372 isolates (Fig. 4a) clearly shows that the differences among the three cephalosporins were most prominent at the lowest MIC values. Cefepime and ceftobiprole were remarkably similar across the spectrum of MIC values, whereas ceftazidime MICs consistently resulted in lower cumulative percentages.

Analysis of the sub-population of putative ESBL or high-level AmpC β-lactamase (299 of the 372 isolates) non-producers indicated that ceftobiprole and cefepime had cumulative percentages of 100% inhibition across almost the entire spectrum of MIC values (Fig. 4b). Among the 21 isolates that were putative AmpC producers but not ESBL producers (Fig. 4c), cefepime and ceftobiprole maintained moderate activity (MIC_{90} values of 8 mg/L for cefepime and 32 mg/L for ceftobiprole), unlike ceftazidime, which demonstrated an $MIC_{50} > 32$ mg/L. Sub-analysis of the 42 putative ESBL-producing isolates showed poor inhibitory activity for all three cephalosporins (Fig. 4d). Therefore, ceftobiprole demonstrates antibacterial activity against the Enterobacteriaceae that resembles that of cefepime more closely than that of ceftazidime.

Similar results have been reported by others. Hebeisen *et al*. [6] showed high levels of in-vitro activity for ceftobiprole against ESBL-negative isolates of Enterobacteriaceae, *Haemophilus influenzae*, *Neisseria gonorrhoeae* and *Moraxella catarrhalis*, among others. Susceptibility was comparable to that of other β-lactams tested.

Ceftobiprole is also active against non-fermenting Gram-negative bacteria, such as *P. aeruginosa*

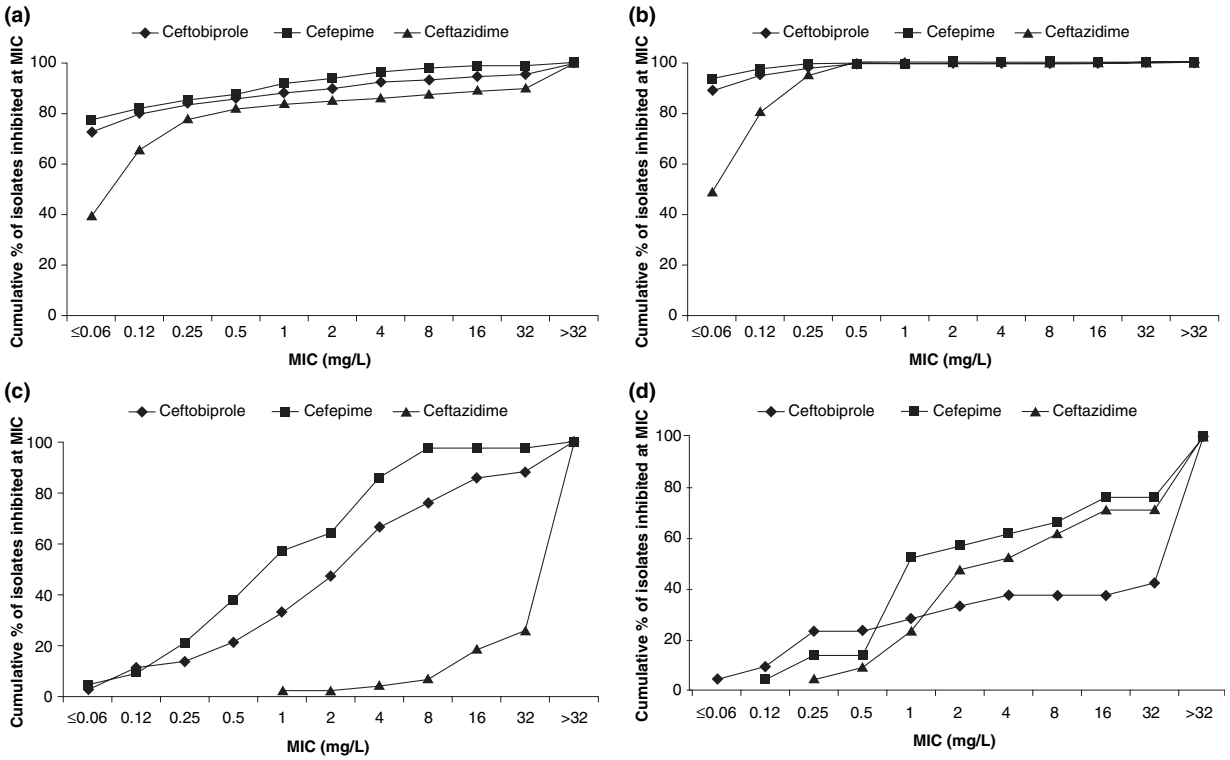

Fig. 4. Cumulative percentages of Enterobacteriaceae isolated from respiratory specimens inhibited at different cephalosporin MIC values for (a) all clinical isolates ($N = 372$), (b) only non-ESBL/AmpC producers ($n = 299$), (c) putative AmpC producers ($n = 21$), and (d) putative ESBL producers ($n = 42$). Isolates tested were *Escherichia coli* ($n = 60$), *Serratia marcescens* ($n = 62$), *Klebsiella pneumoniae* ($n = 60$), *Enterobacter cloacae* ($n = 60$), *Enterobacter aerogenes* ($n = 17$), *Citrobacter freundii* ($n = 20$), *Citrobacter koseri* ($n = 7$), *Klebsiella oxytoca* ($n = 25$) and *Proteus mirabilis* ($n = 61$) (15th ECCMID, abstract P-1569).

and *Acinetobacter baumannii*. The susceptibility of *P. aeruginosa* to ceftobiprole was evaluated *in vitro* using collections of recent clinical isolates from the USA ($n = 203$) and Europe ($n = 204$) in comparison to β-lactams commonly used to treat pseudomonal infections (43rd IDSA, abstract P-506). β-Lactam resistance was common within both collections. MIC_{90} values against European isolates were 32 mg/L for ceftobiprole, compared to >32 mg/L for ceftazidime and >128 mg/L for piperacillin–tazobactam. Results were similar for isolates from the USA: MIC_{90} of 16 mg/L for ceftobiprole, 32 mg/L for ceftazidime, and >128 mg/L for piperacillin–tazobactam. Graphical representations of the cumulative percentages of *P. aeruginosa* isolates inhibited over a range of MIC values show similar profiles for ceftobiprole and ceftazidime, which are superior to that of piperacillin–tazobactam (Fig. 5). Similar results have been obtained in other studies (44th ICAAC, abstract E-2021) [6,9]. For example, in a recent study (44th ICAAC, abstract E-2021), ceftobiprole had MIC_{90} values against *P. aeruginosa* isolates ($n = 101$) of 16 mg/L (range 1–32 mg/L), as compared to 16 mg/L (range 1 to >65 mg/L) for cefepime and 32 mg/L (range 1 to >64 mg/L) for ceftazidime. Like all other β-lactams, ceftobiprole does not show activity against strains producing metallo-β-lactamases.

Acinetobacter spp. are also among the Gram-negative, non-fermenting bacteria commonly isolated from nosocomial infections. In-vitro activity of ceftobiprole against *A. baumannii* is potentially clinically relevant, since MDR strains have been isolated with increasing frequency in recent years (44th ICAAC, abstract E-2021). Ceftobiprole activity was compared to that of other cephalosporins among isolates obtained during pneumonia clinical trials performed in 1998–2001 (44th ICAAC, abstract E-2021). Among the 42 *A. baumannii* isolates, ceftobiprole activity was superior to that of other cephalosporins (Fig. 6). Ceftobiprole

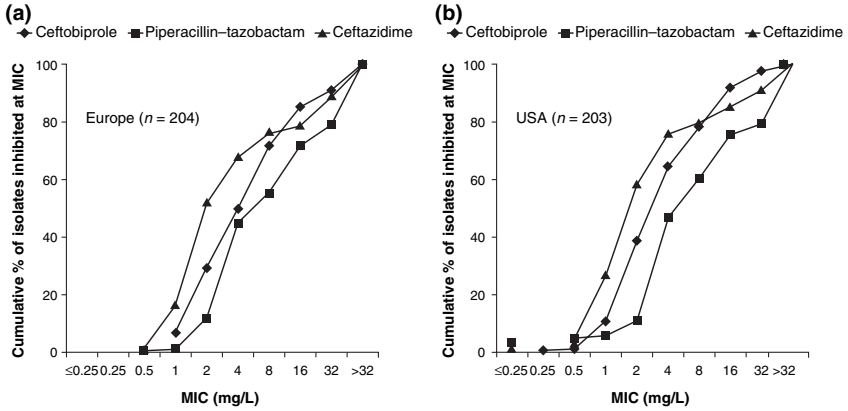

Fig. 5. Cumulative percentages of *Pseudomonas aeruginosa* isolates over a range of MIC values for ceftobiprole, ceftazidime and piperacillin–tazobactam in (a) Europe and (b) the USA (43rd IDSA, abstract P-506).

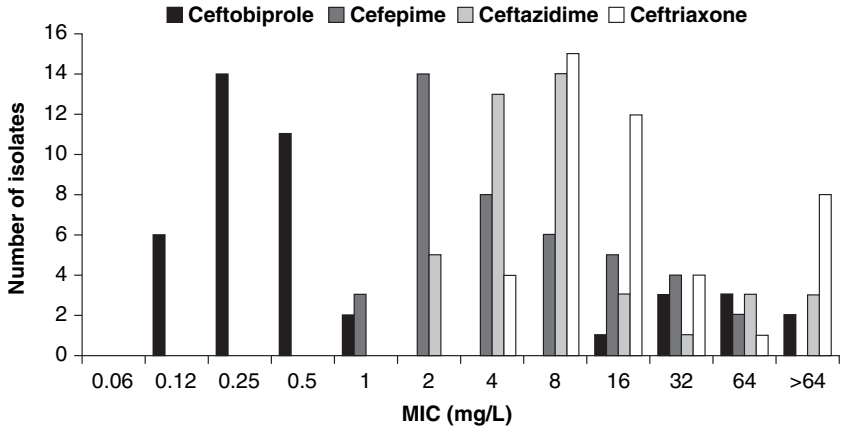

Fig. 6. In-vitro antibacterial activity of ceftobiprole and other cephalosporins against *Acinetobacter baumannii* (44th ICAAC, abstract E-2021).

inhibited 79% of isolates at 4 mg/L, compared to 60% for cefepime, 43% for ceftazidime, and 5% for ceftriaxone. Interestingly, isolates had a bimodal distribution with regard to susceptibility to ceftobiprole (Fig. 6). One sub-population was fully susceptible, with MIC values ranging from 0.13 to 1 mg/L. A separate, multidrug-resistant sub-population had MIC values ranging from 16 to >64 mg/L. This population includes strains producing multiple β-lactamases, including metallo-β-lactamases, to which ceftobiprole is not stable.

IN-VITRO ACTIVITY AGAINST ANAEROBES

Ceftobiprole activity against anaerobic bacteria has also been examined. Some *Clostridium* species were found to be relatively susceptible to ceftobiprole, with MIC_{90} values of <4 mg/L [9]. Modest activity (MIC_{50} < 4 mg/L and MIC_{90} > 4 mg/L) was reported against Gram-positive anaerobic cocci and species from the following genera: *Actinomyces*, *Clostridium*, *Fusobacterium*, *Lactobacillus*, *Porphyromonas*, *Prevotella*, and *Veillonella* [14]. However, *Bacteroides fragilis* and other *Bacteroides* species were generally resistant to ceftobiprole [6,9,14].

CEFTOBIPROLE AND B-LACTAM RESISTANCE

In considering these data with regard to known β-lactam resistance mechanisms, ceftobiprole has certain advantages over penicillins and other extended-spectrum cephalosporins [9] (15th ECCMID, abstract P-1569; 45th ICAAC, abstract C1-55). Most important is that only ceftobiprole is relatively unaffected by resistance mediated by acquired or mutated PBPs, judging from its high binding affinity for *S. aureus* PBP2′ and *S. pneumoniae* PBP2x [6,15]. The exception is *Enterococcus faecium* PBP5, against which no available β-lactam is effective.

Ceftobiprole is also stable in the presence of certain β-lactamase-mediated resistance mechanisms. Unlike penicillins, ceftobiprole is unaffected by *Staphylococcus* penicillinases and broad-spectrum β-lactamases (TEM-1 derivatives). Like extended-spectrum cephalosporins, ceftobiprole appears to have modest stability against the AmpC β-lactamases, as described earlier [6]. In addition, Queenan and Bush (45th ICAAC, abstract C1-55) and Heep *et al*. (15th ECCMID, abstract P-1569) demonstrated that ceftobiprole had a low potential for inducing chromosomal AmpC β-lactamase and that it was a poor substrate for hydrolysis by this enzyme in the Gram-negative isolates tested (*Morganella morganii*, *Citro. freundii*, *Providencia stuartii*, *Enterobacter cloacae*, *S. marcescens*, *P. aeruginosa*), similar to cefepime and ceftazidime. However, ceftobiprole appears to be hydrolysed by most ESBLs and metallo-β-lactamases, as demonstrated by Hebeisen *et al*. [6].

IN-VIVO EFFICACY OF CEFTOBIPROLE

The efficacy of ceftobiprole against infections caused by a wide range of pathogens, including MRSA and other resistant strains, has been demonstrated in multiple animal models, including those mimicking severe systemic infection. These experimental systems include mouse septicaemia, subcutaneous abscess and pneumonia models; rat endocarditis and tissue cage models; and rabbit endocarditis and osteomyelitis models.

In experimental septicaemia, ceftobiprole activity was comparable to or better than that of ceftriaxone, cefepime and meropenem [6]. In-vivo efficacy, measured as ED_{50} (dose at which 50% of animals survived on the fourth day following infection), correlated well with MIC values determined *in vitro*. Ceftobiprole was effective against numerous clinical strains of MSSA, MRSA, group A *Streptococcus*, penicillin-sensitive *S. pneumoniae*, and penicillin-resistant *S. pneumoniae*, with ED_{50} values ranging from <0.2 to 2.4 mg/L. For non-ESBL-producing Gram-negative species, ceftobiprole had ED_{50} values ranging from <0.2 to 4.0 mg/L for *E. coli*, *K. pneumoniae*, *C. freundii*, *Enterobacter cloacae*, *S. marcescens*, *P. mirabilis*, and *P. aeruginosa*. Ceftobiprole was inactive against infections caused by *Proteus vulgaris*, as expected due to production of a broad-spectrum class A cephalosporinase that also hydrolyses cefepime and ceftriaxone [6,16].

The effectiveness of ceftobiprole was evaluated in a mouse model of subcutaneous abscesses induced using two MRSA strains, including an intermediately vancomycin-resistant *S. aureus* strain. Ceftobiprole had superior bactericidal activity as compared with vancomycin and linezolid [6]. Ceftobiprole was similarly active in rat and rabbit endocarditis models using MRSA [17,18].

Mouse models have demonstrated the effectiveness of ceftobiprole against pneumonia. Leukopenic mice were treated with subcutaneous injections of ceftobiprole or ceftriaxone starting 3 h after infection with a *S. pneumoniae* strain that was either penicillin-susceptible, penicillin-resistant or penicillin/ceftriaxone/cefotaxime-resistant [19]. Ten-day survival rates for ceftobiprole and ceftriaxone were statistically significantly different for only one penicillin-resistant strain, with a difference favouring ceftobiprole (93% vs. 13%, $p < 0.0001$). Ceftobiprole required much lower doses than ceftriaxone to achieve comparable survival rates. In a similar murine system, ceftobiprole was as effective as cefepime and ceftriaxone against infections caused by *H. influenzae*, *Enterobacter cloacae*, and non-ESBL-producing *K. pneumoniae* (44th ICAAC, B-1177).

The effectiveness of ceftobiprole in MRSA-induced osteomyelitis, a particularly difficult infection to treat, has been evaluated in rabbits. Ceftobiprole administration resulted in 100% clearance of the infection, with good drug penetration into the bone matrix and marrow (45th ICAAC, B-2007).

These data indicate that ceftobiprole is equivalent or superior to comparators against MRSA, intermediately vancomycin-resistant *S. aureus* and non-ESBL-producing Gram-negative bacteria in many classic animal models.

CONCLUSION

The microbiological profile of ceftobiprole shows a distinct cephalosporin that acts as a potent inhibitor of bacterial PBPs, including *S. aureus* PBP2′ and *S. pneumoniae* PBP2x. This potent inhibition accounts for the superior in-vitro activity of ceftobiprole against MRSA compared with other available β-lactams, with in-vitro activity equivalent to linezolid and vancomycin (MIC 2 mg/L). The activity of ceftobiprole against *P. aeruginosa* is

similar to that of ceftazidime and piperacillin–tazobactam. In addition, ceftobiprole has broad-spectrum microbiological activity against many other Gram-negative and Gram-positive pathogens. MIC values are typically ≤4 mg/L for most Gram-positive pathogens (including MRSA and penicillin-resistant *S. pneumoniae*), for >90% of the Enterobacteriaceae, and for >50% of *P. aeruginosa* and *Acinetobacter* species.

Multiple classic animal models mirror this equivalence or superiority to comparators against a wide range of pathogens, including resistant ones such as MRSA and penicillin-resistant *S. pneumoniae*. The broad-spectrum in-vitro and in-vivo activity suggests that ceftobiprole has potential for empirical use in suspected Gram-negative and Gram-positive infections, including those due to resistant organisms such as MRSA.

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